REMARKS

Please find submitted with this response a Revocation of Power of Attorney with New Power of Attorney and Change of Correspondence Address (Form PTO/SB/82) and Assignee's Statement under 37 CFR 3.73(b) (Form PTO/SB/96). Entry of same is requested and all future correspondence on this application should be directed to the address associated with Customer No. 31096.

The Office Action mailed August 12,2003, has been received and carefully reviewed. Reconsideration and withdrawal of the rejections of the claims of the above- identified application is respectfully requested, a Petition for One (1) Month Extension of Time accompanying this paper.

Restriction Requirement

Applicants hereby affirm the election of Group I, claims 25-34.

Claim Objection

Claim 28 is objected to because of an informality. However, the phrase "wherein the at least one amino acid" is actually necessary to properly distinguish the subject of the sentence, which is "at least one amino acid." Deleting "the", and ignoring the prepositional phrase starting with "of the H-helix..." for illustrative purposes, would result in a sentence reading "wherein at least one amino acid ...is in the region of amino acids 304-314." Such a claim would be indefinite and would not further limit the independent claim.

Rejection Under 35 U.S.C. §101

Claims 25-34 are rejected because the claimed invention is directed to nonstatutory subject matter. The claims have been amended to recite an "isolated" modified antithrombin protein. This amendment is supported by the specification as originally filed, for example at pages 17-18. No new matter has been added. Applicants submit that the claims, as amended, do

assert the presence of the "hand of man" and are thus directed to a statutory category of invention. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 25-29 and 31-34 are rejected as failing to comply with the written description requirement. The Examiner asserts that the four antithrombin mutants shown in the specification do not provide an adequate written description of the claimed invention. Applicants respectfully traverse the rejection.

The claims are directed to modified antithrombin proteins in which one or more amino acid in the H-helix is modified to have a more positive charge as compared to non- modified antithrombin. As stated by the Examiner, the specification provides examples of four specific modifications. Applicants submit that the four specific examples provide adequate written description of the claimed invention. MPEP 2163.02 states that the standard for determining compliance with the written description requirement is based on whether or not the specification conveys that he or she was in possession of the invention; that possession can be shown by including a description of an actual reduction to practice; and that the subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement. As acknowledged by the Examiner, the instant specification provides an actual reduction to practice of the invention by providing examples of four mutations that result in the modified protein being claimed. Based on the specific examples, it is clear that Applicants were in possession of the invention as claimed. Additionally, Applicants submit that the four examples do provide a representative number of examples to show that they were in possession of the genus of claim 25.

The Examiner's reliance on the Emmerich article is not understood. The instant specification does describe how to product the claimed modified antithrombin proteins, and does provide specific examples of mutations that achieve the claimed modifications. The instant specification describes how to make the claimed invention, and provides an actual reduction to practice in the form of specific examples, thus the specification does provide an adequate written description of the claims.

The Examiner asserts that, regarding claim 29, none of the AT-mutants or SEQ ID #s in the specification represent or show a peptide containing substituted arginine (R) in positions 309,310,312 or 313 as claimed. The Examiner's attention is directed to page 10, lines 20-23, where the specification recites an embodiment involving "replacing one or more of amino acids 309, 310, 312, and 313 with a positively charged amino acid, such as lysine (K) or arginine (R), preferably K." Thus, the specification clearly provides a written description of the invention of claim 29.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 25, 28, and 31-34 are rejected as being indefinite. Regarding claim 25, the specification describes the invention as an antithrombin with an H-helix region that is modified to increase its overall positive charge. The specification then goes on to describe various ways the overall positive charge may be increased, including substituting a negatively charged amino acid with a neutral or positively charged amino acid, substituting a neutral amino acid with a positively charged amino acid, or insertion of positively charged amino acids or deletion of negatively charged amino acids. See page 10, lines 12-19. Thus, the specification defines the modified protein as having an H-helix with a more positive charge as compared to the non-modified protein. Claim 25 encompasses either a net charge change from neutral to positive or a net charge change from negative to neutral. Both embodiments are described and contemplated by the specification. Applicants submit the claim is not ambiguous because the determination of "more positive charge" is made in comparison to the charge of the H-helix of the non- modified protein. The claims must be read in light of the specification, and the instant specification provides clear examples and definitions of how the H-helix of antithrombin is modified to alter the charge. Therefore, the claims are not ambiguous when read in light of the specification.

Claims 31 and 32 are rejected as being indefinite. The claims have been amended to recite a pharmaceutically acceptable carrier. Support for the amendment is found in the specification as filed, for example at page 12, lines 1-6.

Rejections Under 35 U.S.C. §103(a)

Claims 25-34 are rejected as unpatentable over Jakubowski in view of Shirk. Jakubowski is asserted as teaching that inhibitory effects of antithrombin on thrombin is reduced because of conformational changes that occur after formation of the thrombin- thrombomodulin (T-TM) complex, but does not teach any way to increase the affinity of antithrombin for thrombin after the T-TM complex is formed. Shirk is relied on for teaching that substituting the basic and positively charged amino acids in the H-helix of protein C inhibitor (PCI) with neutral and negative amino acids leads to a decrease in the interaction of PC and heparin that results in a decrease in inhibitory effect of PCI on T-TM. The Examiner states that the combination of Jakubowski and Shirk results in an antithrombin molecule with increased inhibitory activity towards the T-TM complex because the H-helix of antithrombin has been modified to resemble that of PCI. Applicants respectfully traverse the rejection.

As stated in MPEP 2143, the three basic requirements of a *prima facie* case of obviousness are: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The Examiner has not met this burden.

The Examiner has provided no motivation based on the knowledge generally available to one of ordinary skill in the art to combine the teachings of Jakubowski and Shirk. The Examiner's assertion that when the references are combined, the result is the claimed invention does not satisfy any of the above requirements for making a basic case of *prima facie* obviousness. The Examiner merely states that once the references have been combined, the claimed invention has been achieved. No indication of <u>why</u> one would be motivated to even try combining the teachings of Jakubowski and Shirk has been provided. Furthermore, combining the teachings of the cited references provides only the basic knowledge that thrombomodulin alters thrombin specificity once the T-TM complex is formed, and that the major heparin-binding site of PCI is the H-helix, as opposed to the D-helix heparin-binding site of antithrombin.

In addition, the combined teachings fail to teach or suggest all of the limitations presently recited in Applicants' claims. For example, the cited references taken alone or in combination do not provide an isolated modified *antithrombin* protein having an H-helix in which at least one amino acid has been modified to have a more positive charge than an H-helix of a non-modified antithrombin, as recited in Applicants' claims. The presently claimed invention is simply not shown or suggested by the cited references, taken alone or in combination.

Additionally, no reasons have been given for why one of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of the cited references. While Jakubowski and Shirk provide information regarding the T-TM complex and the role of the H-helix in heparin binding for PCI, absolutely no teaching is provided in either reference to suggest any portion of the PCI-related teaching may be applied in analogous fashion to the antithrombin situation. It is far beyond an obvious design choice to "superimpose" the PCI-related teachings on the antithrombin molecule to provide the presently-claimed modified antithrombin proteins. As the *prima facie* requirements for an obviousness rejection have not been met, withdrawal of the rejection is respectfully requested.

It is respectfully submitted that each of the presently pending claims is in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby. Respectfully submitted,

Respectfully submitted,

GODFREY & KAHN, S.C.

Date: Nov. 21, 2003

By: _____
Charles L. Leeck, Reg. No. 50,343

Attorneys of Record for Applicant
GODFREY & KAHN, S.C.
780 North Water Street
Milwaukee, WI 53202-3590
Tel.: 414-273-3500
Fax: 414-273-5198
Email: cleeck@gklaw.com
MW766095_1.DOC